Appendix A

Evidence Tables for Team-Based Care Interventions for Hypertension

Literature Used for Estimation of Treatment Effects on Blood Pressure

To derive causal impacts applicable to the U.S., we excluded studies that did not have a RCT design (48 study arms excluded) or were conducted outside of the U.S. (46 study arms excluded). To match our hypothetical intervention design, we excluded studies that did not require uncontrolled hypertension for inclusion (146 study arms excluded). Under these three criteria, 17 study arms remain; however, one additional study was excluded because changes in SBP were unreported.[74] Among the included studies, follow-up periods range from 3 to 12.8 months, but all follow-up periods were included in our 12-month estimated effect. Study sizes ranged from 36 to 519 participants.

Appendix Table A1. Summary of Studies Considered for Team-Based Care for Hypertension Intervention Effects

First author	Year	Uncontrolled hypertension?	Independent medication management?	Sample size	Follow-up	Mean SBP change
Edelman[38]	2010	Yes	Yes	239	12.8m	-7.3
Green[39]	2008	Yes	Yes	519	12m	-8.9
Hill[40]	2003	Yes	Yes	264	12m	-7.1
Hunt[41]	2008	Yes	Yes	460	12m	-5
Magid[42]	2011	Yes	Yes	283	6m	-6
Magid[31]	2013	Yes	Yes	348	6m	-12.4
Margolis[32]	2013	Yes	Yes	388	12m	-9.7
Vivian[44]	2002	Yes	Yes	53	6m	-14.1
Bodgen[33]	1998	Yes	No	95	6m	-12
Borenstein[34]	2003	Yes	No	197	12m	-11
Bosworth (Arm 2)[35]	2011	Yes	No	296	12m	-2.4
Bosworth (Arm 3)[35]	2011	Yes	No	294	12m	-4.3
Carter[36]	2008	Yes	No	179	9m	-8.7
Carter[37]	2009	Yes	No	402	6m	-12
Mehos[43]	2000	Yes	No	36	6m	-10.1
Zillich[45]	2005	Yes	No	117	3m	-4.5

Notes: The uncontrolled hypertension column refers to whether uncontrolled hypertension was required for inclusion in the study. The independent medication management column indicates whether the study protocol allowed the team care providers to independently make changes to a patient's hypertension medication regimen. SBP, systolic blood pressure; m, months

Literature Used for Estimation of Treatment Effects on Lipids

Applying similar exclusion criteria as for blood pressure effects, 14 arms were from studies conducted outside the U.S. and 17 had a non-randomized design, leaving 16 studies that were RCTs conducted in the U.S. Among these studies, 11 involved an intervention with a medication management component, but two report outcomes only in terms of rates of lipid control.[40,75] One additional study was excluded because it has no discernible team component to its intervention.[76] Of the remaining eight studies, four report effects on LDL and HDL cholesterol,[46,47,49,52] two report effects on LDL only,[48,50] one reports effects on total cholesterol only,[77] and one reports effects on total and HDL cholesterol.[51]

None of the studies reporting effects on cholesterol meet the inclusion criteria for hypertension effects described above; therefore, none of the remaining evidence directly corresponds to the potential secondary lipid effects of team-based interventions targeting individuals with uncontrolled hypertension.

For including lipid effects in our secondary analysis, we required that these effects be modeled through changes in LDL or HDL cholesterol. This eliminated the study that reports only on total cholesterol.[77] Of the remaining seven studies (summarized in Appendix Table A2),[46-52] hypertension is an optional inclusion criterion for four of these studies,[46-48,50] a required inclusion criterion for one study,[51] and an implicit inclusion criterion for one more study (through cardiovascular disease risk scoring).[49] The seventh study required diabetes for inclusion.[52] Among includes studies, sample sizes ranged from 141 to 525 participants and follow-up periods ranged from nine to 12 months.

Appendix Table A2. Summary of Included Studies Reporting Lipid Effects From Team-Based Care for Hypertension

First author	Year	Sample size	Follow-up	Mean SBP change	Mean LDL change	Mean HDL change
Allen[46]	2011	525	12m	-6.2	-15.9	0.4
Becker[47]	2005	364	12m	-6.0	-15.5	0.0
Fiscella[48]	2010	282	12m	-2.7	-3.2	N/R
Haskell[49]	2006	141	12m	-10.0	-14.0	4.0
Katon[50]	2010	211	12m	-5.1	-6.9	N/R
Litaker[51]	2003	157	12m	N/R	N/R	2.6
Scott[52]	2006	149	9m	-5.5	-11.2	0.7

N/R, Not Reported; m, months; SBP, systolic blood pressure; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

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Appendix B

ModelHealth: CVD Technical Documentation

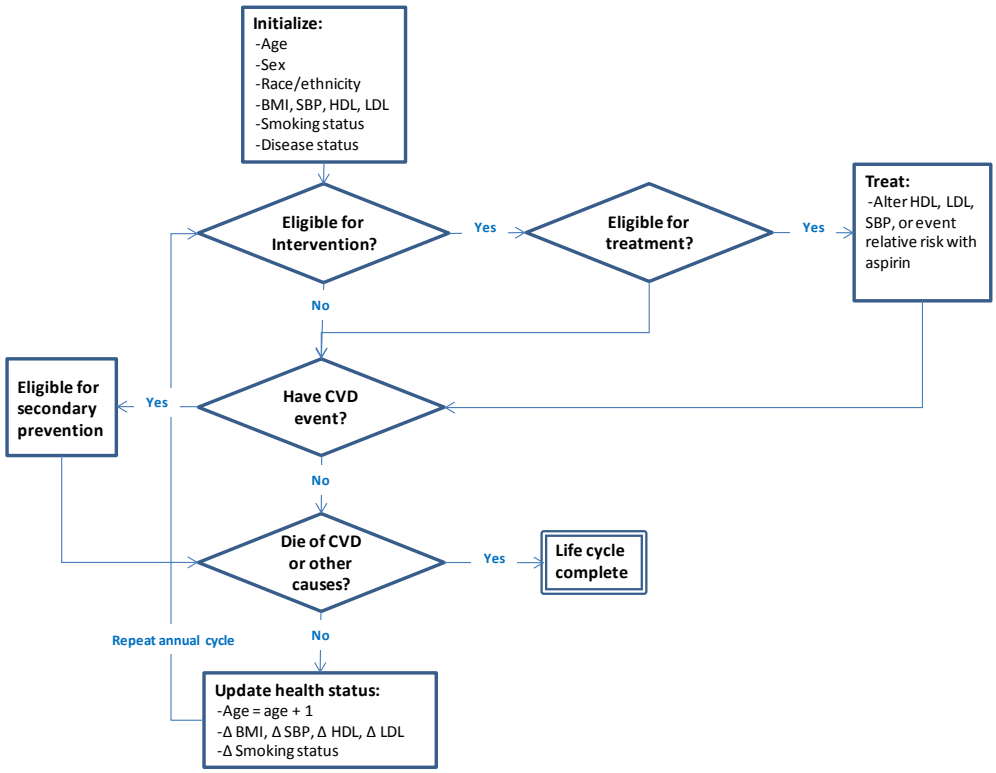
Introduction

This study was conducted using an adapted version of the HealthPartners Institute for Education and Research ModelHealth™: Cardiovascular disease microsimulation model. ModelHealth: CVD is a collection of scientific evidence-based parameters, mathematical functions, and procedural logic—implemented using Visual Basic 6 and Microsoft Excel—designed to evaluate cardiovascular disease prevention policies at the population level. The primary unit of observation in this model is a hypothetical person who takes on a variety of detailed attributes (such as age, sex, race/ethnicity, BMI, systolic blood pressure, disease status, etc.). The lifetime progression of these characteristics is simulated over time. Epidemiological data sourced from the Framingham Heart Study—a major cardiovascular disease surveillance study ongoing since 1948—plays an important role in this model's construction.

Although the mechanics of ModelHealth: CVD center on individuals—i.e., through microsimulation—policy relevance is achieved through aggregating a sufficient number of individuals to be representative of a policy-relevant group, such as the U.S. population. ModelHealth: CVD can be scaled easily to simulate the lifetime progression of hundreds, thousands, or even millions of individuals. Policy interventions are evaluated by simulating the same population twice—once with the policy intervention of interest, such as a clinical preventive service, imposed, and once without it. In practice, this evaluation approach is comparable to a RCT design, with the treatment and the placebo being applied to the same hypothetical research population.

Model Overview

Appendix Figure B1. ModelHealth: CVD flow diagram



Initialization

Figure B1 illustrates the process flow of ModelHealth: CVD. Each new simulation iteration first involves initializing a hypothetical person at a specific age (e.g., 35), with individual characteristics (such as sex and race/ethnicity) and initial health parameters (such as cholesterol and blood pressure levels and BMI) all drawn from U.S.-representative distributions. Thereafter, ModelHealth: CVD simulates the hypothetical person's lifespan and the natural history of cardiovascular disease in annual cycles.

Interventions and Background Preventive Services

At the beginning of each annual cycle, the model determines whether the simulated individual receives a specified intervention of interest or a background preventive service. Background preventive services in ModelHealth: CVD are screening for hypertension, screening for lipid disorders, and aspirin counseling, as recommended by the U.S. Preventive Services Task Force.[78-80] Eligibility for preventive services may be dictated by the parameters of a policy intervention—such as aspirin use among all persons older than age 40 without prior history of GI bleeding or hemorrhagic stroke in the treatment arm—or by contemporary adoption patterns of background preventive services (i.e., applied to both policy arms) observed in the population. Upon receiving a preventive service, the model determines whether the individual is eligible for treatment (e.g., taking statins for treating high cholesterol). Pharmacological treatment criteria for dyslipidemia and hypertension are implemented to be consistent with the Adult Treatment Panel III[13] and the JNC-7[81] guidelines, respectively.

Treatment

The effect of treatment for high cholesterol or high blood pressure is realized through its impact on high- and low-density lipoprotein cholesterol (HDL-C/LDL-C) or systolic blood pressure (SBP), respectively. For example, an individual with high cholesterol could be treated with a statin and see a 30% reduction in LDL and a 10% increase in HDL, but taking a statin does not translate to a direct reduction in the individual's risk of a myocardial infarction. Instead, these changes will translate to lowered risk of disease, as determined by the customized risk engine described in the following section. In contrast, taking aspirin on a daily basis directly alters the relative risk of having an event (such as a myocardial infarction or a gastrointestinal bleed).

Disease Events

The next step in each annual cycle (following potential exposure to an intervention and background prevention services and treatment) is to determine whether the individual experiences any non-fatal disease events during that year. Specifically, a person may: (a) have a myocardial infarction, (b) have an ischemic stroke, (c) have a hemorrhagic stroke, (d) experience angina pectoris, (e) develop congestive heart failure, (f) develop intermittent claudication, (g) develop diabetes, and/or (h) experience a gastrointestinal bleed. The annual risks of (a)-(g) are determined by equations derived specifically for this model using data from the Framingham Heart Study.[7,8] If a person has a cardiovascular event—that is, one or more of (a)-(f)—and survives, that person becomes eligible for secondary prevention. Treatment for dsylipidemia and hypertension for secondary prevention similarly based on ATP III and JNC-7 guidelines, respectively, and men and women who have a non-fatal myocardial infarction or ischemic stroke are also eligible for aspirin chemoprophylaxis.

In each annual cycle, a person also faces a risk of dying from cardiovascular disease or from other causes. The annual risk of death from CVD-related causes also is based on a study-specific equation derived from the Framingham Heart Study. The probability of dying from a cause other than CVD or cancer is derived from U.S. life tables[82] and compressed mortality data in the CDC Wonder database.[83] A person who dies of any cause—or reaches the age of 100—exits the model, with the person's lifecycle complete.

Aging and Progression of Natural History

Finally, when a person survives a cycle, that individual's health status and parameters must be transitioned for the next cycle. Each cycle is annual, and therefore, the individual's age will

simply increment by one. Biological cardiovascular risk factors—namely, HDL, LDL, SBP, and BMI—naturally progress over time, and annual transitions are modeled by a two-step process. First, it is determined whether the individual's risk factor increases, decreases, or stays the same. These probabilities are based on a multinomial logistic equation (which accounts for age, previous values, and other individual characteristics). Second, if a specific risk factor is determined to increase or decrease, a secondary set of equations determines the size of this change. The process repeats itself until the simulated person dies (or reaches age 100). Tobacco initiation and cessation probabilities are derived from National Health Interview Survey data[10] and published estimates from longitudinal studies.[11,12]

Model Data Sources and Parameters

A computational model with the degree of detail contained within ModelHealth: CVD requires a considerable amount of data and scientific evidence to specify all necessary parameters and inform the key transitional mechanisms. This lengthy section describes all the data sources (and in some cases, assumptions) required for the model to operate.

Parameter Initialization

Each iteration of ModelHealth: CVD begins with the initialization of a new representative individual to simulate. Initial demographic characteristics, including age, sex, race/ethnicity, and U.S. Census region, are derived from the American Community Survey three-year sample.[73] Lifetime education, employment status, poverty status, and initial insurance status are derived from the combined 2009-2012 Current Population Surveys.[20] Initial CVD risk factors, including BMI, SBP, LDL, and HDL are derived from the combined 2001-2010 National Health and

Nutrition Examination Survey (NHANES) surveys.[14-18] Diabetes and prior CVD status at model initialization also are derived from the combined NHANES surveys. Initial smoking status is derived from the 2007 National Health Interview Survey[10] and calibrated to estimates by the Congressional Budget Office,[84] as described in further detail below. Baseline characteristics of the simulated U.S. population cross-section are presented in Appendix Table B1.

Appendix Table B1. Baseline Characteristics of Simulated U.S. Population Cross-Section (Ages 35+)

	All (N=162.8 million)	Source
SBP (mean, mmHg)	126.1	NHANES [14-18]
% over goal	20.6%	NHANES [14-18]
% treated	22.0%	NHANES [14-18]
Treated SBP (mean, mmHg)	142.0	NHANES [14-18]
% treated over goal	45.7%	NHANES [14-18]
Age		NHANES [14-18]
35-44	25.3%	ACS 3yr [73]
45-54	27.5%	ACS 3yr [73]
55-64	22.6%	ACS 3yr [73]
65-74	13.4%	ACS 3yr [73]
75+	11.2%	ACS 3yr [73]
% female	52.4%	ACS 3yr [73]
Education		
High school or less	44.3%	CPS [20]
Some college	25.6%	CPS [20]
4-year degree or more	30.0%	CPS [20]
Employment status		
Employed	57.1%	CPS [20]
Unemployed	4.9%	CPS [20]
Not in the labor force	37.9%	CPS [20]
Poverty status		
<150%	11.5%	CPS [20]
150%-399%	4.9%	CPS [20]
400%+	83.5%	CPS [20]
% SSI eligible	19.7%	CPS [20]
Insurance status		
Private	53.2%	CPS [20]
Medicaid	3.9%	CPS [20]
Medicare	24.9%	CPS [20]
Uninsured	15.1%	CPS [20]
Other/Multi	2.8%	CPS [20]
BMI (mean, kg/m^2)	29.0	NHANES [14-18]
% overweight	72.4%	NHANES [14-18]
% obese	40.9%	NHANES [14-18]
LDL (mean, mg/dL)	120.3	NHANES [14-18]
% over goal	28.3%	NHANES [14-18]
% treated	22.5%	NHANES [14-18]
% smokers	17.4%	NHIS [10], CBO [84]
% with diabetes	18.7%	NHANES [14-18]
% with previous CVD	12.8%	NHANES [14-18]

SBP, systolic blood pressure; SSI, Supplemental Security Income; LDL, low-density lipoprotein; CVD, cardiovascular disease; NHANES, National Health and Nutrition Examination Survey; ACS, American Community Survey; CPS, Current Population Survey; NHIS, National Health Interview Survey; CBO, Congressional Budget Office

Progression of Biological Risk Factors

After each annual cycle in ModelHealth: CVD, an individual's time-dependent attributes must be transitioned to reflect the age progression and natural history of biological cardiovascular disease risk factors over one's lifetime. A person's age simply increments by one, but the remaining risk factors (BMI, HDL, LDL, and SBP) transition according to a two-step process. Change in smoking status is described in the section below.

Step 1: Determine Probability That a Risk Factor Changes

In the first step of the process, a person faces a probability of increasing, decreasing, or staying the same in a particular risk factor. For LDL, HDL, and BMI, staying the same is defined as a change of +/-1% per year. Due to the greater variability in measuring blood pressure, staying the same in SBP is classified as being within +/-3.5% per year. In all cases, these probabilities were estimated using multinomial logistic regression. HDL, LDL, and SBP were estimated using annualized Framingham Heart Study data adjusting for age, sex, and BMI.[6,7] BMI was estimated from Behavioral Risk Factor Surveillance System (BRFSS) survey data (from current weight and previous year recall) adjusting for age, sex, and race/ethnicity.[21]

For year-to-year BMI transitions, the increasing or decreasing cases were split in two additional sub-cases. Specifically, one allows for small changes or "drifting" (i.e., an increase or decrease of 1% to 5%), and the other accommodates larger changes (i.e., an increase or decrease of 5% or more). Our analysis of Framingham Heart Study and BRFSS data indicate that these weight-change modalities reflect what people typically experience in real life, and the probabilities of each modality shift as we age. For example, a typical male may be most at risk for significant

weight gain in his 20s, be more likely to have his BMI drift up in his 30s and 40s, and then face a stronger tendency towards weight stabilization in his 50s and 60s.

Step 2: Determine Size of Risk Factor Change

Once a person's transition modality has been determined, the second step is to determine the size of the change. Age, sex, and (in the case of BMI) race/ethnicity-specific equations were estimated for each of these cases. Whereas the first step in the process is stochastically determined in each cycle (i.e., facing a probability of each scenario), the second step is deterministic, with the transition applied as a percentage change (or zero change, in the case that a risk factor remains stable from the previous year). Appendix Table B2 summarizes the details of this two-step process of year-on-year transitions of risk factors.

Appendix Table B2. ModelHealth: CVD Annual Progression of Risk Factors

Step	Case	Source	Controlled factors	Estimator
1	P(BMI Change)	BRFSS[21]	Age, sex, race/ethnicity, previous BMI	Multinominal Logit
1	P(HDL Change)	Framingham[6,7]	Age, sex, BMI, previous HDL	Multinominal Logit
1	P(LDL Change)[a]	Framingham[6,7]	Age, sex, BMI, previous LDL	Multinominal Logit
1	P(SBP Change)	Framingham[6,7]	Age, sex, BMI, previous SBP	Multinominal Logit
2	Q(BMI Change)	BRFSS[21]	Age, sex, race/ethnicity, previous BMI	OLS
2	Q(HDL Change)	Framingham[6,7]	Age, sex, BMI, previous HDL	Random Effects
2	Q(LDL Change)[a]	Framingham[6,7]	Age, sex, BMI, previous LDL	Random Effects
2	Q(SBP Change)	Framingham[6,7]	Age, sex, BMI, previous SBP	Random Effects

[a]In practice, the progression of LDL is more complex than indicated in the table and text. LDL was not measured with the same regularity as HDL and total cholesterol in the Framingham Heart Study; therefore, transitions in LDL were modeled in additional two steps. First, the probability and quantity of change in total cholesterol was modeled as described above. Second, HDL and total cholesterol were used in a prediction equation—derived from NHANES with high explanatory power (i.e., $R2 > 0.9$)—to estimate a corresponding LDL level. Although not included in the prediction equations, estimations related to changes in cholesterol and blood pressure controlled for treatment.

P(), probability; Q(), quantity; OLS, Ordinary least squares regression; BRFSS, Behavioral Risk Factor Surveillance System

Modeling Smoking Behavior

Overview

Individuals may be in one of four smoking states: never smoker, current smoker, recent quitter, or former smoker. The probability that an individual is in a given smoking state at introduction into the model is determined by multivariate risk equations that account for age, sex, race/ethnicity, and the lifetime educational attainment. Similarly, the likelihood that an agent who is currently in the never-smoker state begins smoking within a given cycle is conditioned on his/her age, sex, race/ethnicity, and lifetime educational attainment. Estimates of risk equations used data from the National Health Interview Survey (NHIS).[10]

Initial Smoking Status

A multinomial logistic regression with outcomes corresponding to the four smoking states was used to estimate the likelihood of an individual having an initial smoking status given his/her age, sex, race/ethnicity, and lifetime educational attainment. The estimated distribution across potential smoking states was used to determine each agent's initial smoking status at introduction into the model.

The NHIS does not directly ask respondents about their current smoking status. As such, the following definitions are used:

- Never smoker: Having smoked fewer than 100 cigarettes in their lifetime
- Current smoker: Having smoked at least 100 cigarettes in their lifetime and having smoked in the last week

- Recent quitter: Having smoked at least 100 cigarettes in their lifetime and having quit for less than 4 years
- Former smoker: Having smoked at least 100 cigarettes in their lifetime and having quit for 4 or more years

The usual definitional prerequisite of having smoked at least 100 cigarettes in their lifetime was applied to exclude experimental smoking. The results of the estimation are contained in Appendix Table B3. Time in state (i.e., the number of years as a smoker and/or the number of years since quitting) partially determines the likelihood of quitting or relapsing. An age of initiation is assigned to those initialized as current smokers, recent quitters, or former smokers. For those initialized as recent quitters or former smokers, an age of cessation also is assigned.

Smoking status initialization is implemented in a two-step process. In Step 1, for all agents initialized as a current smoker, recent quitter, or former smoker, a random draw (from a distribution drawn configured to initiation rates estimated from the NHIS) determines the age at which the person first started smoking (e.g., age 19). Then, for those initialized as recent quitters and former smokers (Step 2), a random draw from a second distribution configured to cessation rates estimated from NHIS and truncated at the age of initiation determines the age of cessation (e.g., age 26). These two ages are used to determine the time spent smoking and time since cessation, which are used in the model when determining future smoking behavior.

Appendix Table B3. Results of Multinomial Estimation Predicting Initial Smoking Status

	Current smoker	Former smoker
Ref. category	-0.798	-1.922
Female	-0.453	-0.605
24-44	0.559	1.151
45-64	0.541	1.813
65+	-0.538	2.203
Black	-0.475	-0.714
Hispanic	-1.249	-0.723
Other	-0.702	-0.793
High school	0.688	0.112
Post-secondary	-1.293	-0.394

Source: National Health Interview Survey.[10] Table values represent coefficients in a multinomial logistic regression equation.

Lifetime Smoking Behavior

An individual's "risk" of changing smoking status (i.e., transitioning to another smoking state), is determined by current state, time in that state, and demographic characteristics. Individuals who have never smoked can either remain in the never smoker state or begin smoking and transition to the current smoker state. A current smoker who is in the current smoker state can remain or quit and transition to the recent quitter state. A recent quitter either remains in the recent quitter state, relapses into the current smoker state, or moves to the former smoker state once four years have passed. A former smoker either relapses into the current smoker state or remains in the former smoker state.

Logistic regression equations determine the risk of smoking initiation or the probability of cessation from NHIS data.[10] We identified quitters as those indicating they had ceased cigarette use within the last 12 months with no indication of relapse. Appendix Table B4 contains the results of these estimations.

Relapse after quitting tobacco use is time-sensitive. The longer a person has successfully quit smoking, the less likely he or she is to relapse. The cross-sectional design of NHIS made estimation of relapse rates that account for time since cessation difficult. Instead, we used published estimates based on longitudinal studies. These values were adjusted during calibration to provide reasonable values of age-, sex-, and race/ethnicity-specific tobacco use rates. Appendix Table B5 contains these rates.

Appendix Table B4. Results of Logistic Regressions Predicting Adult Smoking Status

	Tobacco initiation	**Tobacco cessation**
Ref. category	-27.7099	-1.772
Female	3.5358	-0.046
24-44	9.814	-0.1545
xFemale	-10.0481	-0.00165
45-64	10.441	-0.1181
xFemale	-5.817	0.2346
White	-6.3501	0.2966
xFemale	-3.8882	Not significant
Black	3.4254	-0.0603
xFemale	-3.4627	Not significant
Hispanic	5.0037	0.0776
xFemale	-0.0798	Not significant
No high school	6.5959	-0.00755
xFemale	-3.8882	Not significant
High school	9.2186	0.0191
xFemale	-3.4627	Not significant
Post-secondary	4.5348	0.3067
xFemale	-0.0798	Not significant

Source: National Health Interview Survey.[10]
Note: Table values represent coefficients in a multinomial logistic regression equation.

Appendix Table B5. Baseline Smoking Tobacco Relapse Rates

Years since successful quit	**Probability of relapse**	**Source**
1	0.37	[11]
2	0.08	[12]
3	0.08	[12]
4	0.08	[12]
5	0.08	[12]
6	0.038	[12]
7	0.038	[12]
8	0.021	[12]
9	0.021	[12]
10	0.021	[12]
11	0.005	[12]

Calibration of Smoking Behaviors to CBO Model

Tobacco prevalence was calibrated to reflect baseline tobacco use projections of the Congressional Budget Office (CBO) prior to final analysis.[20] These calibrated initiation and cessation rates are used for all estimates. We were unable to obtain details regarding how the CBO parameterizes specific population groups. Instead, we worked with estimates derived from the 2012 CBO report (Figure 1-1, page 3).[20] Using this figure and the general description of the CBO's approach as a guide, we tested a reasonable set of parameter modifications to adjust the smoking prevalence rates produced by our model over the next 10 years to better reflect CBO's baseline.

Three key sources of deviation from the CBO model were identified and adjusted for within the model. The first source was the estimated initiation patterns from NHIS age-based categories that created a stepped function and subsequent "jagged" initiation patterns. The resolution was to smooth initiation rates using a moving average process across ages that held constant prevalence within each age group. This adjustment removed "jumps" in prevalence among birth cohorts, but initiation remained relatively high. The second source of deviation was that NHIS-based estimates suggest stable or increasing smoking prevalence among young adults and adolescents. Thus, prevalence in the original model differed from the CBO model, which shows a secular trend toward decreasing prevalence over time. The resolution to this issue was to decrease initiation rates across lower age ranges by lowering implied prevalence to 24-year-old prevalence and smoothing using a 10-year moving average process. The effect of this was a lowered prevalence among new birth cohorts that was a closer approximation to initial cohort and a prevalence pattern that approximated those of current 10- to 24-year-olds. This results in a new "steady-state" population prevalence of approximately 13-14%, which is lower than the current

population-wide prevalence. Finally, the third source of deviation was that former smokers exhibited high relapse rates among older age groups (ages 50 or older), causing higher prevalence relative to the CBO model. The approach to resolve this issue was to utilize an exponential distribution, which decreased likelihood of relapse among former smokers, and relapse was eliminated for former smokers older than age 50.

Risk of Cardiovascular Disease Events

Published risk calculators for cardiovascular disease—such as PROCAM,[22] SCORE,[23] QRisk,[24] or those derived from the Framingham Heart Study[25]—generally estimate an individual's 10-year risk of disease. These are difficult to translate to a microsimulation model with annual cycles. In addition, existing risk profiles commonly combine outcomes (such as chronic heart disease or cardiovascular disease, generally, compared to myocardial infarction or ischemic stroke, specifically—for example, see Wilson et al.[26]). The distinction is particularly important for accurately estimating costs associated with disease. They may also exclude potentially policy-relevant risk factors (such as differentiating current smokers from recent quitters or former smokers), and/or include clinical risk factors that may not be salient to population-level policy evaluation (such as left ventricular hypertrophy in the risk of stroke—for example, see D'Agostino et al.[27]). For these reasons, we used primary data from the Framingham Heart Study to derive and develop customized 1-year risk equations for use in ModelHealth: CVD.

We developed risk equations for eight outcomes: myocardial infarction (MI), ischemic stroke, hemorrhagic stroke, angina pectoris, congestive heart failure, intermittent claudication, non-specific cardiovascular disease-related death, and diabetes. The risk analysis uses the Original

Cohort (beginning in 1948 with 5,209 attendees) and the Offspring (beginning in 1971 with 5,124 attendees) arms of the Framingham Heart Study. Data were sourced from the National Heart, Lung, and Blood Institute's (NHLBI's) Biologic Specimen and Data Repository Information Coordinating Center (BioLINCC), with approval and human subjects oversight from the HealthPartners Institute for Education and Research's IRB.[6,7] Statistical survival analysis was performed using Stata, Version 11.

To use as much of this rich data source as possible, allow for time-varying covariates, and provide for a direct estimate of annual risk, we adopted a parametric over the more common semi-parametric Cox proportional hazard approach in our analysis. Similar parametric methods have been previously explored and validated by Framingham Heart Study researchers.[28] Age, BMI, HDL, LDL, SBP, and one's disease history are all included as potential time-varying covariates in the analyses.

Because age accounts for time within a single person's life and because we do not have strong evidence with respect to the impact of secular time trends, we estimated an individual's risk using the exponential proportional hazards model (which has a time independent or "memoryless" property). Specifically, estimation was conducted using the streg command in Stata. Time independence is particularly important when estimating annual risk (i.e., t=1), because the additional information in the shape parameter (i.e., embodied in the so-called accelerated failure time metric) is never appropriately used and may otherwise systematically over-or under-estimate risk in a one year context. The resulting exponential model is estimated with a person j likelihood function of the risk of an event $\left(d_j \in \{0,1\}\right)$ between t_{0j} and t_j is

$$L_j = \left[\frac{e^{\left(-e^{\beta_0+x_j\beta}\right)t_j}}{e^{\left(-e^{\beta_0+x_j\beta}\right)t_{0j}}}\right]\left(e^{-e^{\beta_0+x_j\beta}}\right)^{d_j}$$

with an individual's probability of an event in the next year equal to $F(1) = 1 - e^{\left(-e^{\beta_0+x_j\beta}\right)}$.

Appendix Table B6. Summary of Risk Equations Derived from Framingham Heart Study Data

Risk of first myocardial infarction (MI)			**Risk of angina pectoris (AP)**		
	Hazard ratio	Z-Score		Hazard ratio	Z-Score
Age	1.046	18.15	Age	1.024	9.88
Sex	0.411	-14.25	Sex	0.587	-8.42
HDL	0.985	-6.64	HDL	0.989	-4.62
LDL	1.005	9.99	LDL	1.006	11.95
SBP	1.013	11.17	SBP	1.011	8.90
Smoke	1.701	8.84	Previous CVD	2.750	13.84
Diabetes	2.029	9.46			
Previous CVD	2.798	16.28			
Risk of first ischemic stroke (IS)			**Risk of first congestive heart failure (CHF)**		
	Hazard ratio	Z-Score		Hazard ratio	Z-Score
Age	1.076	20.94	Age	1.074	22.35
HDL	0.988	-4.39	HDL	0.986	-5.49
SBP	1.022	15.63	SBP	1.015	10.65
Smoke	1.724	6.27	BMI	1.024	3.43
Diabetes	1.918	6.90	Smoke	1.401	4.15
Previous CVD	2.243	10.09	Diabetes	2.176	9.92
			Previous MI	3.885	17.76
			Previous Other CVD	1.838	8.22
Risk of first hemorrhagic stroke (HS)			**Risk of diabetes**		
	Hazard ratio	Z-Score		Hazard ratio	Z-Score
Age	1.049	6.64	Age	1.064	30.67
SBP	1.020	5.94	BMI	1.108	20.90
BMI	0.904	-4.75	SBP	1.004	2.91
Smoke	1.497	2.15	HDL	0.968	-13.72
Previous CVD	1.568	2.35			
Risk of intermittent claudication (IC)			**Risk of CVD-related death**		
	Hazard ratio	Z-Score		Hazard ratio	Z-Score
Age	1.039	10.39	Age	1.068	26.50
Sex	0.619	-5.32	Sex	0.569	-10.36
HDL	0.993	-2.01	LDL	1.004	6.04
LDL	1.007	8.35	SBP	1.009	8.95
SBP	1.015	8.65	Smoke	1.676	8.83

Smoke	2.871	12.05	Diabetes	1.403	5.27
Diabetes	2.237	7.20	Previous MI	2.875	17.48
Previous CVD	2.529	9.93	Previous IS	3.546	19.93
			Previous CHF	6.565	30.41
			Previous Other CVD	1.747	9.87

Source: Author's analysis of data from the Framingham Heart Study.[25]
Notes: Estimations are based on the exponential proportional hazards model. All continuous variables used in ModelHealth:CVD are natural log transformed; however, hazard ratios of non-log variables are presented here instead for easier interpretation.

Baseline Risk of GI Bleeding Events

We estimate the baseline risk of gastrointestinal (GI) bleeding events using an analysis of European observational data.[29] Evidence indicates that men face higher risk of GI bleeding than women, and risk for both sexes increases with age. Probabilities for GI bleeding events are summarized in Appendix Table B7 below.

Appendix Table B7. Summary of Risk for GI Bleeding Events in the CVD Prevention Policy Model

	Age 20-59	**Age 60-69**	**Age 70-79**	**Age 80 and older**
Men	0.008	0.0024	0.0036	0.006
Women	0.004	0.0012	0.0018	0.003

Source: [29]
Note: Values represent annual probabilities based the estimated incidence rate (per 1,000 person years) of upper gastrointestinal tract complications.

Utilization of Background Preventive Services

Background rates of screening for lipids and aspirin use in the model are every 5 years in accordance with clinical guidelines.[3,4] We assume that adults have a blood pressure measurement opportunity at least once per year. Good evidence is lacking for the percentage of individuals who would accept prevention screening—in accordance with USPSTF recommendations—when

offered. We assume 90% of individuals will accept any of the USPSTF-recommended clinical preventive services.[1-3] This is implemented as a person-level parameter, such that a person who accepts screening will always do so and one who does not accept, will never do so.

Good and consistent evidence is also lacking for long-term adherence rates among those taking aspirin or drug therapy for the prevention of cardiovascular disease. Treatment adherence rates from clinical trials are generally not representative of the population. Individuals who enroll in a clinical trial are believed to be more motivated to regularly take study drugs, and clinical trial subjects also tend to receive more consistent and intensive attention from healthcare providers than does the general population. Retrospective or claims-based studies capture a more representative population (although, generally biased toward over-representing those with health insurance coverage), but these studies are likely to miss patients who are prescribed treatment but never fill a prescription (i.e., primary non-adherence) and overstate nonadherence for patients lost to other insurers, providers, lost coverage, etc. Due to such limitations, we restrict our assumptions to point estimates of average adherence for primary and secondary prevention.

Adherence rates to aspirin chemoprevention are particularly difficult to estimate because, unlike with statins and antihypertensives, there is no paper trail from a prescription written in a provider's office, to a fill at a pharmacy, and ultimately to a reimbursement claim with an insurer. Counseling advice for a patient to take aspirin is not consistently recorded in medical record systems, nor can over-the-counter purchases of aspirin be readily tracked. Moreover, some patients choose to take aspirin without direction from their physician or medical provider. Under these limitations, we draw our estimates from a nationally representative survey regarding

aspirin use.[30] This survey found 36% of individuals with no history of cardiovascular disease reporting regular aspirin use. Balancing those who may be taking aspirin on their own accord (17% reported use of aspirin despite no discussion with a provider) against those for whom aspirin use may have been counseled due to benefits outweighing the harms (57% in the survey were deemed to be of objective increased risk for cardiovascular disease), we assume in the base case that 50% of patients counseled to aspirin chemopreventive therapy will adhere and that aspirin adherence rises to 70% for secondary prevention (Appendix Table B8).

Evidence regarding differences in adherence to lipid modifying and blood pressure lowering drug therapies is mixed.[31-34] Although factors such as cost (statin therapy is generally more expensive than antihypertensive therapy) and regimen complexity (antihypertensive treatment strategies can often incorporate use of two, three, or even four drugs in combination) could drive differences in adherence in drug therapies, we simplify by assuming similar average adherence between treating lipids and hypertension. Systematic reviews of antihypertensives show long-term adherence (i.e., 2 years or more) ranging typically (varying considerably by drug class) from 30% to 50%, with shorter-term adherence (i.e., 1 year or less) a bit higher.[35,36] A recent review of adherence to statins shows slightly wider estimates in long-term adherence, typically ranging from roughly 20% to 70%.[37] Analyses in both cases suggest prior cardiovascular disease increases likelihood as much as 50%-70%.[37-39] Taking this all into account, we assume 40% adherence to statins and antihypertensives for primary prevention in the base case, and we assume 60% adherence for secondary prevention (Appendix Table B8).

Appendix B8. Summary of Treatment Adherence Assumptions in ModelHealth: CVD

Treatment	Prevention type	Adherence (Base case)
Aspirin	Primary	50%
Aspirin	Secondary	70%
Statins	Primary	40%
Statins	Secondary	60%
Antihypertensives	Primary	40%
Antihypertensives	Secondary	60%

Source: Author's assumptions based on evidence reported in the literature.[30-39]

Treatment Effects of Background Preventive Services

Aspirin for Primary Prevention

The USPSTF aspirin recommendation cites evidence indicating that, when used for primary prevention, aspirin reduces the risk of myocardial infarction for men and ischemic stroke for women.[3] We make use of the same evidence—a meta-analysis of six primary prevention trials[40]—which suggests a 32% (95% OR CI: 0.54-0.86) in myocardial infarction risk in men and a 24% reduction (95% OR CI: 0.63-0.93) in ischemic stroke risk in women. No statistically significant differences in CVD-related or all-cause mortality were found in either men or women when using aspirin for primary prevention.

Because evidence is insufficient to distinguish clear differences between men and women in risk for hemorrhagic stroke and major GI bleeding, we calculated a combined unadjusted OR from the primary prevention trials to estimate the risk of these adverse events associated with aspirin use.[41] We estimate that regular aspirin use raises the risk of hemorrhagic stroke by 42% on average (95% OR CI: 1.05-1.93) and raises the risk of major bleeding by 62% (95% OR CI: 1.38-1.93). In all cases, we draw an individual-specific effect size from a triangle distribution based on the 95% CIs. A summary of the aspirin treatment effects when used for primary prevention of CVD is given in Appendix Table B9.

Appendix Table B9. Summary of Aspirin Treatment Effects (RR) for Primary Prevention of Cardiovascular Disease (CVD)

Condition	Prevention type	Sex	Low	Mid	High
Relative risk of myocardial infarction	Primary	Men	0.86	0.68	0.54
Relative risk of myocardial infarction	Primary	Women	1	1	1
Relative risk of ischemic stroke	Primary	Men	1	1	1
Relative risk of ischemic stroke	Primary	Women	0.93	0.76	0.63
Relative risk of hemorrhagic stroke	Primary	Men	1.05	1.42	1.93
Relative risk of hemorrhagic stroke	Primary	Women	1.05	1.42	1.93
Relative risk of CVD-related death	Primary	Men	1	1	1
Relative risk of CVD-related death	Primary	Women	1	1	1
Relative risk of GI bleed	Primary	Men	1.38	1.63	1.93
Relative risk of GI bleed	Primary	Women	1.38	1.63	1.93

Source: [40]

Aspirin for Secondary Prevention

Aspirin also may be initiated following a non-fatal CVD event for the purposes of reducing the risk of subsequent events (secondary prevention). A recent meta-analysis of 16 secondary prevention aspirin trials indicates a 31% reduction in MI risk (95% Rate Ratio [RR] CI: 0.60-0.80) and a 22% reduction in ischemic stroke risk (95% RR CI: 0.61-0.99).[42] Similar to primary prevention trials, secondary preventive use of aspirin does not show a statistically significant reduction in CVD-related or all-cause mortality.

Due to the relative rarity of hemorrhagic stroke and major GI bleeding and the smaller sample sizes of participants in secondary trials, the estimates of increased risk of adverse events from aspirin in secondary prevention are less precise. Instead of using these less precise estimates, we assume the increased risk of hemorrhagic stroke and GI bleeding from aspirin use in secondary prevention is the same as observed in the primary prevention trials. In all cases, we draw an individual-specific effect size from a triangle distribution based on the 95% CIs. A summary of

the aspirin treatment effects when used for primary prevention of CVD is given in Appendix Table B10.

Appendix Table B10. Summary of Aspirin Treatment Effects for Secondary Prevention of Cardiovascular Disease (CVD)

Condition	Prevention type	Sex	Low	Mid	High
Relative risk of myocardial infarction	Secondary	Men	0.8	0.69	0.6
Relative risk of myocardial infarction	Secondary	Women	0.8	0.69	0.6
Relative risk of ischemic stroke	Secondary	Men	0.99	0.78	0.61
Relative risk of ischemic stroke	Secondary	Women	0.99	0.78	0.61
Relative risk of hemorrhagic stroke	Secondary	Men	1.05	1.42	1.93
Relative risk of hemorrhagic stroke	Secondary	Women	1.05	1.42	1.93
Relative risk of CVD-related death	Secondary	Men	1	1	1
Relative risk of CVD-related death	Secondary	Women	1	1	1
Relative risk of GI bleed	Secondary	Men	1.38	1.63	1.93
Relative risk of GI bleed	Secondary	Women	1.38	1.63	1.93

Source: [40,42]

Statins for Treating Lipids

Due to the overwhelming use of statins (i.e., HMG-CoA reductase inhibitors) in the treatment of high cholesterol—recent estimates suggest rates in excess of 90% of Americans seeking pharmacological treatment[43]—we simplified treatment of dyslipidemia in ModelHealth: CVD to this drug class. We used several recent (and/or otherwise relevant) meta-analyses/reviews of statins to identify major (of 1,000 or more persons) RCTs comparing lipid reduction associated with statins to a placebo.[44-49] Included trials—accounting for a total of 67,815 subjects—had a follow-up period of at least 52 weeks, involved subjects for primary or secondary prevention, were subject-blinded (at a minimum), and reported changes in LDL or HDL cholesterol as an outcome. Trials were excluded if additional (open label) lipid-lowering drugs were allowed for

use in the placebo group (unless observed at rates lower than 10%). The trials included in our analysis are summarized in Appendix Table B11.

Appendix Table B11. Summary of Statin Trials Included in Estimation of Treatment Effects

Trial	Subjects	Ages	Baseline LDL	Baseline HDL	Mean ↓LDL	Mean ↑ HDL
4S	4,444	30 – 70	188.3	45.8	47.1	3.7
AFCAPS/TEXCAPS	6,605	45 – 73	150.4	36.3	41.8	1.9
ALERT	2,102	30 – 75	158.5	52.2	36.7	0
ASCOT-LLA	10,305	40 – 79	133	50.7	46.4	0.8
ASPEN	2,410	40 – 75	113.5	47	33.1	0.9
HPS	20,536	40 – 80	131.5	42.5	50.3	0.8
LIPID	9,014	31 – 75	150	36	37.5	1.8
PROSPER	5,804	70 – 82	146.9	50.3	39.7	2.5
WOSCOPS	6,595	45 – 64	192	44	49.9	2.2

Sources: 4S[50]; AFCAPS/TEXCAPS[51]; ALERT[52]; ASCOT-LLA[53]; ASPEN[54]; HPS[55,56]; PROSPER[57]; WOSCOPS[58]
Notes: LDL and HDL unit measures are in mg/dL.

To accommodate differential drug response according to baseline (only one included trial included stepped treatment in its experimental protocol[50]), we estimated treatment effects on cholesterol levels using a simple weighted ordinary least squares regression, with baseline LDL or HDL levels (respectively) as the only predictor:

$$Effect_{Chol} = \beta_0 + (BaselineChol)\beta_{BaselineChol}$$

The average effect size of statins on LDL was estimated to be a 42.9 mg/dL reduction, with an additional marginal impact of 0.014 mg/dL reduction per mg/dL of baseline LDL. The average effect size of statins on HDL was estimated to be a 2.2 mg/dL increase, with a marginal impact of 0.017 mg/dL reduced effect per mg/dL of baseline HDL. These results indicate that the typical lipid modifying response to statin therapy is not highly sensitive to baseline lipid levels.

To accommodate interpersonal differences in the impact of drug therapy on LDL cholesterol in ModelHealth: CVD, we constructed a triangle distribution centered on the mean effect size described above, with upper and lower limits defined by the SD in effect size observed in statin trials, to draw person-specific effect sizes. We estimated the SD in LDL cholesterol reduction using a meta-analysis of (generally smaller/shorter) placebo controlled trials rather than the major trials summarized in Appendix Table B11, because the primary endpoints in these trials were cardiovascular disease outcomes (and as a result, standard deviations in cholesterol changes were not typically reported). We did find not good evidence on the interpersonal variability of treatment effects from statins on HDL, and we incorporate only mean treatment effects in this case.

Finally, all trials—with exception of WOSCOPS[58]—reported results solely based upon intention-to-treat analyses. The average weighted adherence to the treatment across study arms among included trials reporting this measure was 89.4%. To account for diminished average treatment effects attributable to non-adherence to prescribed therapy, we estimate an appropriate adjustment by dividing lipid impact by 0.9 in the base case. Statin treatment effects in ModelHealth: CVD are summarized in Appendix Table B12.

Appendix Table B12. Summary of Statin Treatment Effects

	β0	βBaselineChol	SD	Adherence adjustment
Statin effect on LDL	42.881	0.014	24.382	0.90
Statin effect on HDL	2.176	-0.017	N/A	0.90

Source: Analysis of clinical trials described in Appendix Table B11.

Antihypertensives for Treating Elevated Blood Pressure

We used recent meta-analyses/reviews of antihypertensive therapy to identify major (of 1,000 or more persons) RCTs comparing blood pressure reduction associated with drug therapy to a placebo.[59-67] Included trials—accounting for a total of 54,863 subjects—had a follow-up period of at least 52 weeks, involved subjects for primary or secondary prevention, were subject-blinded (at a minimum), and reported changes in SBP as an outcome. In addition, due to the considerable heterogeneity in observed blood pressure lowering drug therapy strategies—including differences in first-line drugs, doses, and combinations[68]—we required treatment arm protocol to include stepped therapy (and preferably matched stepped therapy of a placebo in the control arm). Trials were excluded if additional (open label) blood pressure lowering drugs were allowed for use in the placebo group (unless observed at rates lower than 10%). The trials included in our analysis are summarized in Appendix Table B13.

Appendix Table B13. Summary of Antihypertensive Drug Trials Included in Estimation of Treatment Effects

Trial	Subjects	Ages	Baseline SBP	Mean ↓ SBP
FEVER	9,711	50 – 79	154.3	4.5
HYVET	3,845	80+	173.0	13.0
MRC-1	17,354	35 – 64	161.5	10.5
MRC-2	4,396	65 – 74	173.0	15.5
PROGRESS	6,105	30 – 90	147.0	9.0
SHEP	4,736	60+	170.3	14.0
STOP	1,627	70 – 84	195.0	22.0
Syst-China	2,394	60+	170.5	9.1
Syst-Eur	4,695	60+	174.0	13.0

Sources: FEVER[69]; HYVET[70]; MRC-1[71], MRC-2[72]; PROGRESS[73]; SHEP[74]; STOP[75]; Syst-China[76]; Sys-Eur[77]

To accommodate diverse treatment strategies (i.e., stepped and combination) with respect to baseline blood pressure relative to goal, we estimated treatment effects on blood pressure levels

using a simple weighted ordinary least squares regression, with baseline SBP levels (respectively) as the only predictor:

$$Effect_{SBP} = \beta_0 + (BaselineSBP)\beta_{BaselineSBP}$$

The average effect size of antihypertensive drugs on SBP was estimated to be a 40.1 mmHg increase, counterintuitively, but this is offset by an additional marginal impact of 0.31 mmHg reduction per mmHg of baseline SBP (Appendix Table B14). Hence, the intercept on the treatment effect is negative, implying that antihypertensives begin to raise blood pressure around SBP baseline levels of 108 mmHg or lower. In practice, this threshold is well-below standard SBP goals (140 mmHg for most patients, 135 mmHg for diabetics), and such blood pressure raising effects (a statistical anomaly) are not invoked by the model.

To accommodate interpersonal differences in the impact of drug therapy on SBP in ModelHealth: CVD, we constructed a triangle distribution centered on the mean effect size described above, with upper and lower limits defined by the SD in effect size observed in the antihypertensive trials, to draw person-specific effect sizes. The SD of drug treatment on SBP was estimated from the subset of trials from Appendix Table B13 that reported this measure.[70,76,77]

Finally, all trials reported results solely based upon intention-to-treat analyses. The average weighted adherence to the treatment across study arms among included trials reporting this measure was 81.9%. To account for diminished average treatment effects attributable to non-adherence to prescribed therapy, we estimate an appropriate adjustment by dividing lipid impact

by 0.8 in the base case. Average blood pressure lowering effects of antihypertensive drugs used in ModelHealth: CVD are summarized in Appendix Table B14.

Appendix Table B14. Summary of Antihypertensive Drug Treatment Effects

	β0	βBaselineSBP	SD	Adherence adjustment
Antihypertensive drug effect on SBP	-40.101	0.310	16.90	0.80

Source: Analysis of clinical trials described in Appendix Table B13.

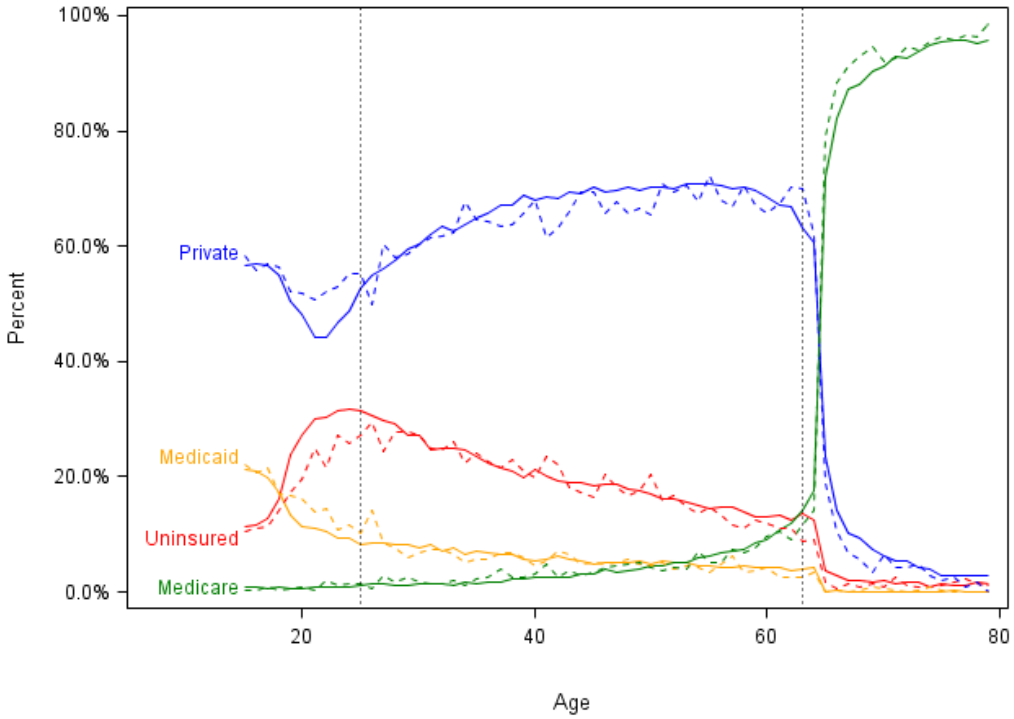
Modeling Insurance Status

As described in above, a person's initial insurance status (i.e., for the first year of the model) is assigned by multinomial logistic regression based on age, sex, race/ethnicity, lifetime education, poverty status, disability status, labor force status, and Census region, as estimated from March Current Population Survey (CPS) data, pooled across years 2009-2012.[14] Based on these characteristics, individuals are assigned to one of five insurance categories: private, Medicaid, Medicare, uninsured, and other insured. Due to small cell sizes in the available data sets, those who are dually eligible for Medicaid and Medicare are assigned to Medicare as the primary payer rather than estimated as a separate insurance category.

Individuals may transition to a new primary payer each year, based on probabilities determined by multinomial logistic regression equations estimated from the three years of observations of the 2008 Cohort of the Survey of Income and Program Participation (SIPP).[78] The determinants of insurance transitions include age, sex, and race/ethnicity and may include disability status and labor force status (varying by age group as indicated by data). As applicable, transitions into and out of disability are first estimated, followed by labor force transitions. Due to known policy-related discontinuities in insurance status at particular ages, the logistic regressions to assign initial insurance status and transition probabilities were run separately for two age strata: 26-64

years and ages 65 and older. Appendix Figure B2 presents a comparison of insurance status by age in the model after 10 years of transitions compared to the contemporary CPS reported rates use for model initialization.[14]

Appendix Figure B2. Validation of insurance status in baseline model population after 10 years.



Notes: Solid lines represent data from the Current Population Survey.[14] Dashed lines represent insurance status proportions in the baseline model population after 10 years from model initialization.

Costs of Disease

Costs of cardiovascular disease and diabetes in ModelHealth:CVD were estimated through analysis of individual-level Medical Expenditure Panel Survey (MEPS) data. To improve estimates—particularly, among less common events such as hemorrhagic stroke—data from the

2001-2012 surveys[79] were combined and appropriately weighted, with costs deflated to 2012 dollars. We differentiated costs associated with an incident event (and those subsequently accrued during the year of the incident event) from ongoing costs from a previous event. Incident and ongoing costs due to diabetes could not be distinguished in the MEPS survey, and we assumed these costs could be reasonably averaged across the duration of a diabetes diagnosis. In all cases, costs were derived from estimated actual expenditures (rather than recorded charges). We apportion costs by payer using an insurance sub-model that assigns each simulated individual to a primary payer: private insurance, Medicaid, Medicare (including Medicare/Medicaid dual-eligibles), uninsured, or other/multiple insurance. We limited our analysis of costs to those of age 35 and older.

Incident (First-Year) Costs

To identify all costs associated with the first-year of an incident cardiovascular event, we first combined total person-level expenditures across several major categories tracked by MEPS, including: inpatient hospital stays, outpatient visits, office-based medical provider visits, emergency room visits, prescribed medicines, home health expenses, and other medical expenses. Costs associated with dental visits were represented the only expenditure category tracked by MEPS which was not included in our analysis. Expenditures associated with lipid or blood pressure therapy were excluded (because our analysis includes these costs separately).

To identify incidence of a new event, we assumed that inpatient hospital stays indicated a significant event had occurred during that year. We used ICD9 coding to identify incident events associated with myocardial infarction (ICD9 410), ischemic (ICD9 434) or hemorrhagic stroke (ICD9 430, 421, or 432), angina pectoris (ICD9 413), congestive heart failure (ICD9 428), and

intermittent claudication (ICD9 440). Diabetes status of individuals was determined by the combination of self-report, clinical encounters (either inpatient, outpatient, emergency, or office-based) with a primary coding of diabetes (ICD9 250), and prescription claims for diabetic medications.

Due to issues common to the analysis of healthcare costs—in particular, rare but extremely high cost events and heteroscedastic errors—we fit these data to a generalized linear model (GLM) with a log link function and gamma distributed variance. Specifically, adding controls for age, sex, and diabetes status, we fit the following model:

$$\text{Total Expenditures} = \beta_0 + (\text{age})\beta_{\text{age}} + (\text{sex})\beta_{\text{sex}} + (\text{diabetes})\beta_{\text{diabetes}} + (\text{MI})\beta_{\text{MI}} + (\text{IS})\beta_{\text{IS}} + (\text{HS})\beta_{\text{HS}} + (\text{AP})\beta_{\text{AP}} + (\text{CHF})\beta_{\text{CHF}} + (\text{IC})\beta_{\text{IC}}$$

where incident disease events, such as myocardial infarction (MI), are coded as dummy variables corresponding to observed inpatient stays (as described above). Marginal disease expenditures were estimated by estimating the difference in population average costs with and without that disease (i.e., the marginal value at population means).

Ongoing Costs

To identify all ongoing costs associated with a previous cardiovascular event, we first combined total person-level expenditures across several major categories tracked by MEPS, including: inpatient hospital stays, outpatient visits, office-based medical provider visits, emergency room

visits, prescribed medicines, home health expenses, and other medical expenses. As with the case of incident events, costs associated with dental visits were excluded. Expenditures associated with lipid or blood pressure therapy were also excluded (because our analysis includes these costs separately).

To identify previous events, we used a combination of self-reported status (e.g., *Have you ever been told by a medical provider that you had a heart attack or myocardial infarction?*) and coding of office-based medical encounters. We used ICD9 coding to identify ongoing care associated with myocardial infarction (ICD9 410), ischemic or hemorrhagic stroke (ICD9 434, 430, 421, or 432), angina pectoris (ICD9 413), congestive heart failure (ICD9 428), and intermittent claudication (ICD9 440). So as not to double-count costs included in our analysis of incident events, those with an inpatient encounter during the survey year were not included among those deemed to have had a previous event. As with the case of incident event costs, diabetes status of individuals was determined by the combination of self-report, clinical encounters (either inpatient, outpatient, emergency, or office-based) with a primary coding of diabetes (ICD9 250), and prescription claims for diabetic medications.

As with our analysis of incident event costs, we fit these data to a generalized linear model (GLM) with a log link function and gamma distributed variance. Specifically, adding controls for age, sex, and diabetes status, we fit the following model:

$$\text{Total Expenditures} = \beta_0 + (\text{age})\beta_{\text{age}} + (\text{sex})\beta_{\text{sex}} + (\text{diabetes})\beta_{\text{diabetes}} + (\text{MI})\beta_{\text{MI}} + (\text{IS})\beta_{\text{IS}} + (\text{HS})\beta_{\text{HS}} + (\text{AP})\beta_{\text{AP}} + (\text{CHF})\beta_{\text{CHF}} + (\text{IC})\beta_{\text{IC}}$$

where previous disease events, such as myocardial infarction (MI), are coded as dummy variables as described above. Marginal disease expenditures were estimated by estimating the difference in population average costs with and without that disease (i.e., the marginal value at population means).

Diabetes

In our analysis of costs associated with diabetes, we do not distinguish expenditures that are incident to diagnosis or ongoing, and we assume these costs may be reasonably averaged across the duration of disease. As with our cost analyses of CVD events, we determined an individual's diabetes status by the combination of self-report, clinical encounters (either inpatient, outpatient, emergency, or office-based) with a primary coding of diabetes (ICD9 250), and prescription claims for diabetic medications.

We combined total person-level expenditures across several major categories tracked by MEPS, including: inpatient hospital stays, outpatient visits, office-based medical provider visits, emergency room visits, prescribed medicines, home health expenses, and other medical expenses. Costs associated with dental visits and expenditures associated with lipid or blood pressure therapy were excluded. Cardiovascular disease status was identified as either having had an incident or previous event (as described above).

As with our cost analyses of CVD events, we fit these data to a generalized linear model (GLM) with a log link function and gamma distributed variance. Specifically, adding controls for age, sex, and diabetes status, we fit the following model:

$$Total\ Expenditures = \beta_0 + (age)\beta_{age} + (sex)\beta_{sex} + (diabetes)\beta_{diabetes} + (MI)\beta_{MI} + (IS)\beta_{IS} + (HS)\beta_{HS} + (AP)\beta_{AP} + (CHF)\beta_{CHF} + (IC)\beta_{IC}$$

where current or previous disease events, such as myocardial infarction (MI), are coded as dummy variables as described above. Marginal disease expenditures were estimated by estimating the difference in population average costs with and without that disease (i.e., the marginal value at population means).

Costs by Insurer-Type

Estimating costs using the methods above and stratifying by insurer type is not viable due to the small sizes observed among the rarer disease conditions within the MEPS surveys. Therefore, we adjusted the costs for all insurance types, as described above, by using a multiplier calculated as the cost per case ratio for an insurance type divided by the cost per case ratio across all insurance types for CVD events, incident and ongoing. These multipliers for incident CVD costs are 1.26 for private insurance, 0.88 for Medicare, 0.66 for Medicaid, 0.62 for the uninsured, and 0.90 for other or multiple types of insurance. These multipliers for ongoing CVD costs are 1.21 for private insurance, 0.78 for Medicare, 0.88 for Medicaid, 0.51 for the uninsured, and 0.77 for other or multiple types of insurance. Similarly, these multipliers for diabetes costs are 0.73 for private insurance, 0.75 for Medicare, 1.00 for Medicaid, 0.61 for the uninsured, and 1.07 for

other or multiple types of insurance. For disease cases with large cell sizes, this multiplier approach yielded very similar results to those estimated directly. A summary of the final costs by disease and insurance-type can be found in Appendix Table B15 below.

Appendix Table B15. Summary of Disease Costs in ModelHealth: CVD

	Incident costs					Ongoing costs				
	Private	Medicare	Medicaid	Uninsured	Other	Private	Medicare	Medicaid	Uninsured	Other
MI	$46,689	$32,598	$24,585	$22,878	$33,333	$3,004	$1,952	$2,186	$1,277	$1,927
Stroke	$22,896	$15,986	$12,057	$11,220	$16,347	$6,501	$4,225	$4,730	$2,762	$4,170
AP	$30,572	$21,346	$16,098	$14,981	$21,826	$5,142	$3,342	$3,741	$2,185	$3,298
CHF	$37,844	$26,423	$19,928	$18,545	$27,019	$13,974	$9,082	$10,167	$5,938	$8,964
IC	$24,109	$16,833	$12,695	$11,814	$17,212	$7,908	$5,140	$5,754	$3,360	$5,073
Diabetes	$3,976	$4,069	$5,450	$3,293	$5,833	$3,976	$4,069	$5,450	$3,293	$5,833

Notes: Ongoing costs are exclusive of drug therapy costs for high cholesterol or hypertension; these costs are accounted for separately in the ModelHealth: CVD.

Productivity Losses

Four primary sources of productivity losses due to disease and productivity gains due to prevention are incorporated into the model: (1) premature mortality, (2) lost production due to exit from labor force, (3) absenteeism, or days of lost productivity not associated with exit from labor force, and (4) "presenteeism" associated with being at less-than-full working capacity. Each of these categories can have two dimensions: lost labor force productivity and lost non-labor force productivity. Non-labor force productivity could be further divided into time spent producing goods and services outside the formal labor market, and time spent in leisure activity. We limited our attention to lost labor force productivity and time spent producing services outside of the labor force.

We are aware of no single framework that has fully captured each of these components. Perhaps the closest is the approach taken by the Congressional Budget Office to estimate the difference in earnings between never, current, and former smokers.[80] This approach has the potential to capture differences in productivity across all dimensions, to the extent that lost productivity is

reflected in long-term employee earnings. Productivity outside the workplace is excluded by that approach, and earnings reflect only the portion of workplace productivity gains captured by employees in their paychecks. We implemented an approach that combines the highest-quality literature sources available to estimate potential productivity gains from prevention policies, including workplace and household productivity.

Productivity Due to Premature Mortality

In ModelHealth: CVD, individuals may experience premature death from cardiovascular disease. The difference between age of death with and without intervention determines the number of years of premature mortality. We valued the productivity of each year of life using estimates by age group (not differentiated by sex) reported by Grosse et al.[81] updated through 2012 for changes in national average of employee earnings and benefits.[82] These productivity estimates are summarized in Appendix Table B16.

The estimates of Grosse et al.[81] include household productivity reported separately from workplace productivity, as measured by market compensation that includes employee pay and benefits. Both household and market productivity estimates are included in ModelHealth: CVD. These estimates reflect the average of those in and out of the labor force. We therefore we apply them to all individuals in the models, regardless of employment status, to obtain accurate population averages from model results. These estimates exclude the second category: lost production due to exit from the labor force.

Appendix Table B16. Annual Productivity of the U.S. Population

Age	Per person annual market compensation	Per person annual household production value	Per person total annual production value
35–39	$51,843	$18,683	$70,526
40–44	$53,865	$17,699	$71,564
45–49	$54,297	$16,207	$70,505
50–54	$53,480	$14,745	$68,225
55–59	$43,855	$15,709	$59,564
60–64	$31,612	$16,440	$48,052
65–69	$11,334	$17,498	$28,831
70–74	$6,021	$17,264	$23,285
75–79	$3,131	$16,389	$19,521
80+	$1,754	$12,999	$14,753

Source: [81,82]
Notes: Average annual productivity estimates are in 2012 U.S. dollars.

Productivity Lost Due to Absenteeism and Presenteeism

Few estimates of absenteeism and presenteeism are available across multiple conditions in a generalizable population. Mitchell and Bates[83] estimated combined absenteeism and presenteeism costs in one million employees for 13 conditions and four risk factors, based upon Work Limitations Questionnaire (WQL), but they did not report absenteeism and presenteeism costs separately. Mitchell and Bates[83] adjusted salary and benefit valuation upward by a factor of 1.6 to reflect the 'multiplier' impact of absenteeism and presenteeism on work team performance as estimated by Nicholson et al.[84] This multiplier is still reflected in our adjusted estimates, and a more recent analysis suggests that compensating efforts by the ill employee in off-work hours and by coworkers may more than offset the negative impact of a team member on productivity of the rest of the work team.[85]

Several adjustments were needed to apply these estimates of absenteeism and presenteeism costs to the model. Mitchell and Bates[83] reported average days lost across all age groups (ages 18-70). In ModelHealth: CVD, virtually all disease occurs after age 35. In order to improve internal

consistency between disease occurrence, disease costs and productivity costs, we assign zero absenteeism and presenteeism costs to ages 15-34, and we reapportion all absenteeism and presenteeism days to the 35+ age group. Another issue was that Mitchell and Bates[83] estimated the average days per employee; in comparison, Grosse et al.[81] reported average market productivity across all adults employed and not employed. To implement these estimates in the same manner in the model, we adjusted Mitchell and Bates' estimates downward by multiplying them by the portion of the U.S. population ages 25 to 64 who are employed. This allows us to apply the estimates of absenteeism and presenteeism to all individuals in the model, regardless of employment status, without overstating population effects. This in analogous to how population average market and household productivity estimates from Grosse et al.[81] are applied to all individuals, regardless of labor market status, as described above. Population-wide effects from the model are accurate, but the model does not have the ability to accurately report productivity measures stratified by labor status. We also adjusted estimates to 2012 dollars and added productivity growth over time in the same manner described above for productivity losses associated with premature mortality. Inputs and final estimates of absenteeism and presenteeism corresponding to these adjustments are shown in Appendix Table B17.

Appendix Table B17. Average Productivity Losses in the U.S. due to Absenteeism and Presenteeism

	Heart disease	Diabetes
Average annual productivity loss due to absenteeism and presenteesim (ages 35-70)	$359	$355

Source: [81,82]
Notes: Productivity losses due to absenteeism and presenteeism are in 2012 U.S. dollars.

Model Validation

Baseline rates of CVD events are generated by the combination of population characteristics at model initiation, the model's estimation of the natural progression of CVD risk factors as individuals age, and the model's risk equations for disease. Appendix Table B18 below presents prevalence rates of myocardial infarction and ischemic stroke generated by the model for a birth cohort starting at age 40 and compares these values to corresponding rates observed in NHANES[15-19] as a benchmark for the external validity of the ModelHealth: CVD natural history engine.

Appendix Table B18. Comparison of Baseline Modeled CVD Event Rates With National Prevalence Estimates

	Myocardial infarction		Ischemic stroke	
	NHANES (2001-2010)	ModelHealth: CVD	NHANES (2001-2010)	ModelHealth: CVD
	Percent of population with history of prior event			
Men and women				
Age 40-49	1.5%	2.3%	1.6%	1.7%
Age 50-59	4.0%	4.7%	2.3%	2.6%
Age 60-69	8.4%	8.5%	5.9%	4.8%
Age 70-79	12.0%	13.2%	9.3%	10.0%
Men only				
Age 40-49	1.7%	3.0%	0.8%	1.0%
Age 50-59	5.4%	6.4%	2.2%	2.0%
Age 60-69	13.1%	11.6%	6.1%	4.1%
Age 70-79	18.7%	18.7%	8.9%	9.7%
Women				
Age 40-49	1.3%	1.6%	2.4%	2.4%
Age 50-59	2.7%	3.1%	2.5%	3.2%
Age 60-69	4.6%	5.9%	5.8%	5.4%
Age 70-79	7.4%	9.3%	9.6%	10.2%

Notes: This table compares CVD prevalence at various ages between NHANES 2001-2010 combined data and results from the ModelHealth: CVD model. The model run represented here is based on a birth cohort, starting at age 40, with hypertension screening and treatment, cholesterol screening and treatment, and aspirin for primary and secondary prevention all implemented and adopted at contemporary rates. For comparison purposes of the cross-sectional and longitudinal datasets, outcomes are calculated for the age range from NHANES and the mid-point of the age range from the ModelHealth: CVD output; this methodological difference can explain some small discrepancies.
NHANES, National Health and Nutrition Examination Survey; CVD, cardiovascular disease

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